Effects on coagulation of intravenous crystalloid or colloid in patients undergoing peripheral vascular surgery†

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Background. This study investigated whether haemodilution-enhanced coagulation can be demonstrated under regional anaesthesia, whether this occurs before surgery, and whether the fluid used influences the effect.

Methods. Patients were randomly allocated to receive either crystalloid or colloid intravenous fluid. An epidural was administered. Samples of venous blood were taken before fluid administration, after completion of the epidural and initial fluid load, during surgery before heparin, and after 24 h. Thrombelastograph® analysis was performed, and full blood count, international normalised ratio, activated partial thromboplastin time, D-dimers and thrombin–antithrombin complex were measured.

Results. In the crystalloid group, enhanced coagulation compared with baseline was demonstrated after initial fluid load (mean (SD) r-time 10.1 (4.9) min; $P<0.033$; k-time 3.5 (1.7) min; $P<0.01$; α-angle 54.9 (13.9) degrees; $P<0.01$) and before heparin administration (r-time 8.8 (3.9) min; $P<0.01$; α-angle 54.9 (12.6) degrees; $P<0.02$). There was no enhancement of coagulation in the colloid group. There were no changes from baseline after 24 h.

Conclusions. This study confirms that the enhanced perioperative coagulation mechanism is related to dilution, rather than surgery, and is triggered by *rapid* crystalloid haemodilution. Consideration should be given to the use of colloid rather than crystalloid solutions for rapid fluid loading in vasculopathic patients undergoing surgery.

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We have previously demonstrated, *in vitro*[1] and *in vivo*,[2] that haemodilution with 0.9% saline and other crystalloid solutions[3] causes enhanced coagulation as measured using Thrombelastograph® analysis and routine coagulation studies. Numerous other authors have confirmed this.[4–7] The colloids are highly effective volume expanders but there has been a recurring question about their effects on coagulation. However, many of the studies that comment on the effects of colloids on coagulation have used a crystalloid control[8–10] or have not made allowance for any crystalloid the patient was given in addition to the colloid, for example, cardiopulmonary bypass pump prime.[11 12] Popov-Cenic and colleagues[13] have referred to the effect. Vinnazzer and Bergmann[14] compared coagulation in two groups before and after surgery, one treated with hydroxyethyl starch and the other with isotonic saline in the perioperative period. Their findings showed a hypercoagulable state after surgery in the control (saline) group, and an insignificant change in the hydroxyethyl starch group. However, because they only tested coagulation after surgery, it is difficult to determine if the enhanced coagulation was the result of the saline therapy or the surgery. Similarly, the apparently normal coagulation profile in the hydroxyethyl starch group could be interpreted as either a negligible effect of the starch on coagulation, or as an impairment of surgery-induced enhanced coagulation. A review of the decreased incidence of thrombotic events in patients undergoing peripheral vascular surgery under epidural anaesthesia did not comment on the role of intravenous fluids or the influence of surgical stress response on coagulation.[15]

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Table 1 Patient characteristics in the two groups. Data are mean (SD or range) for averaged data. Sample 1 was taken before fluid loading, Sample 2 immediately following fluid loading and placement of regional block, and Sample 3 during surgery, immediately before administration of heparin. *$P<0.03$

	Crystalloid	Colloid
Age (yr)	63.0 (45–77)	58.1 (33–76)
Sex (male/female)	16/4	15/5
Time difference Sample 2–3 (operating time) (min)	92.6 (38.5)	88.9 (33.4)
Co-load Sample 1–2 (litres)	1.0	0.5
Volume infused during surgery, Sample 2–3 (litres)	1.6 (0.8)	1.2 (0.4)
Total volume infused, Sample 1–3 (litres)	2.6 (0.8) *	1.7 (0.4) *

While haemodilution-related coagulation enhancement is of great interest, it has not yet been demonstrated whether it is relevant in a clinical setting and whether the effect occurs on the basis of a stress response or on the basis of the haemodilution-induced enhancement of coagulation. We have therefore performed a controlled *in vivo* study investigating the now established and well-described effects of intravenous fluid on coagulation in peripheral vascular surgery under regional anaesthesia. Furthermore, we investigated whether haemodilution-induced enhancement of coagulation is demonstrable after fluid administration, before surgical stimulus, or only after the surgery has begun; and whether the nature (crystalloid or colloid) of the fluid used has an influence on the effect.

Methods

The University of Cape Town Research Ethics Committee approved this study. Patients considered for inclusion in the study were those presenting for peripheral vascular surgery on the lower limb who were suitable for regional anaesthesia and who gave informed consent for both the regional anaesthetic and the study. Patients were excluded from the study if they were already receiving intravenous fluids at the time of arrival in theatre, if they had received aspirin or any non-steroidal anti-inflammatory drug in the previous 7 days or if they were receiving any anticoagulant medication. Once informed consent had been obtained, patients were randomly allocated to either a colloid or crystalloid intravenous fluid group, using a sequence determined from tables of random numbers.

All subjects received premedication of oral temazepam 10 or 20 mg 1 h before surgery. When the patient arrived in the operating theatre, an intravenous cannula was inserted into a suitable forearm vein. A 20G cannula was inserted into a suitable vein on the opposite forearm for blood sampling. An intravenous infusion of either crystalloid (Plasmalyte B® or modified Ringer's lactate) 1000 ml or hydroxyethyl starch (Haes-steril®) 500 ml was commenced. The choice of crystalloid was made on the basis of the diabetic state of the patient, Plasmalyte B being used in diabetic patients and modified Ringer's lactate (from which calcium is excluded) in the remainder. All patients received an epidural anaesthetic consisting of 0.5% bupivacaine administered through an epidural catheter inserted at a suitable lumbar intervertebral space. No additional sedative agents were administered, and if the regional analgesic technique was inadequate, the patient was excluded from the study. The volume of bupivacaine used initially was 10–12 ml, with subsequent top-up doses administered as necessary to achieve and maintain a sensory level at T10 or above. Approximately half the volume of the fluid load was administered before commencement of the regional block, and the remainder of fluid infused during the performance of the epidural. Hypotension requiring the administration of vasopressor agents was also a post-hoc exclusion criterion. Once a satisfactory block was established, the patient was transferred to the operating room and surgery was commenced. During surgery, patients received only crystalloid or colloid depending on their group, but the volume of fluid infused was judged against clinical criteria of fluid requirement. Blood samples were taken before the administration of any intravenous fluid (Sample 1; baseline), after completion of both the regional anaesthetic and the initial fluid load (Sample 2), during surgery immediately before heparin administration and arterial clamping (Sample 3) and 24 h after the administration of the regional block (Sample 4). Thrombelastograph® analysis and the following tests were performed: full blood count, international normalized ratio (INR), activated partial thromboplastin time (aPTT), D-dimers and thrombin–antithrombin (TAT) complexes.

All samples were taken following a 5 ml blood flush to remove contaminants from the sampling site.

Results

The two groups were similar with respect to age, sex and the time taken between Samples 1 and 3. The volume of fluid used during surgery before cross-clamp was greater in the crystalloid group than in the colloid group (Table 1). A comparable degree of haemodilution was achieved in the two groups, as demonstrated by an equivalent decrease in haematocrit of approximately 10% in both groups. In the crystalloid group, a faster onset of coagulation, an increase in the rate of clot formation and an increase in clot strength were demonstrated after the initial fluid load (Sample 2) as well as just before heparin (Sample 3), using Thrombelastograph® analysis (r- and k-times decreased, maximum amplitude increased). No enhancement of coagulation was observed in the colloid group (Table 2). No changes from baseline were evident after 24 h (Sample 4) in either group.

The between-group difference in Thrombelastograph® values compared with control shows a statistically significant difference in r-time at the time of Sample 3 ($P<0.005$) and in k-time at sample 2 ($P<0.03$). There was a significant between-group difference in change from baseline in α-

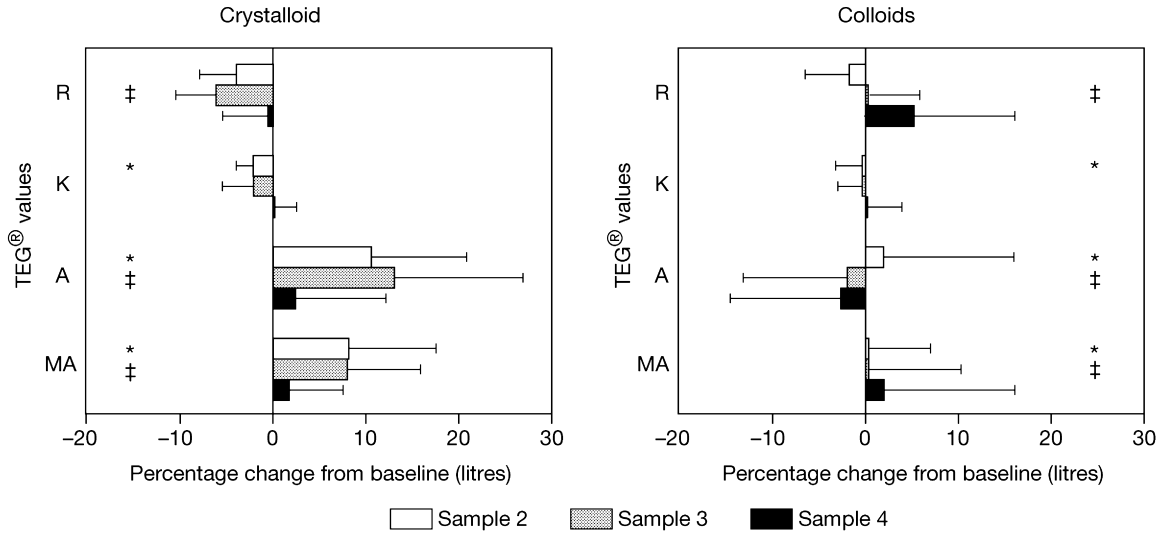

Fig 1 Between-group comparison of changes in Thrombelastograph® (TEG®) values from Sample 1 (baseline – before fluid loading). Sample 2 was taken immediately following fluid loading and placement of regional block; Sample 3 during surgery, immediately before administration of heparin and Sample 4 24 h after at the start of surgery. Data are mean (SD). R, r-time; K, k-time; A, α-angle; MA, maximum amplitude. **P*<0.03, ‡*P*<0.005.

Table 2 Within-group analysis of changes in Thrombelastograph® variables from baseline (Sample 1). **P*<0.05 compared with sample 1. NS, not significant

Sample	r-time (min)		k-time (min)		α-angle (°)		Maximum amplitude (mm)		Haematocrit (%)	
Crystalloid										
	Mean (SD)	***P****	**Mean (SD)**	***P****	**Mean (SD)**	***P****	**Mean (SD)**	***P****	**Mean (SD)**	***P****
1	14.0 (5.8)		5.7 (2.6)		43.6 (15.1)		54.6 (14.5)		42.4 (6.2)	
2	10.1 (4.9)	0.033	3.5 (1.7)	0.013	54.9 (13.9)	0.014	62.6 (13.3)	NS	38.2 (7.6)	0.044
3	8.8 (3.9)	0.010	4.0 (3.1)	NS	54.9 (12.6)	0.022	64.2 (11.1)	NS	36.8 (6.3)	0.014
4	13.6 (7.6)	NS	5.7 (3.3)	NS	46.3 (14.9)	NS	55.0 (16.4)	NS	35.6 (6.0)	0.002
Colloid										
	Mean (SD)	***P***	**Mean (SD)**	***P***	**Mean (SD)**	***P***	**Mean (SD)**	***P***	**Mean (SD)**	***P****
1	11.3 (4.3)		5.4 (2.5)		46.2 (12.1)		51.9 (15.1)		42.5 (5.8)	
2	9.6 (3.7)	NS	5.1 (2.6)	NS	46.7 (11.3)	NS	52.0 (15.2)	NS	37.9 (7.7)	0.047
3	11.5 (4.0)	NS	5.1 (2.5)	NS	44.5 (12.4)	NS	51.3 (13.0)	NS	34.4 (6.7)	0.001
4	15.1 (11.1)	NS	5.4 (2.8)	NS	43.6 (13.2)	NS	54.7 (15.1)	NS	34.6 (8.7)	0.001

angle at Sample 2 (*P*<0.03) and a greater difference at Sample 3 (*P*<0.005). The changes in maximum amplitude from control demonstrate a significant between-group difference at Sample 2 (*P*<0.005) and Sample 3 (*P*<0.03). There were no between-group differences in change from baseline in Sample 4 (Fig. 1).

The INR was significantly increased in the colloid group compared with the crystalloid group at Sample 3 (*P*=0.025), but there were no differences in aPTT at any time (Table 3). There were no significant within-group changes.

There was no significant change from control in TAT and D-dimers in either group (Fig. 2).

Table 3 International normalized ratio (INR), and activated partial thromboplastin time (aPTT) at various sample times. Data are mean (SD). P values give between-group differences. There were no within-group differences. NS, not significant

	Sample	Crystalloid	Colloid	*P* value
INR	1	1.2 (0.2)	1.3 (0.3)	NS
	2	1.2 (0.3)	1.4 (0.4)	NS
	3	1.2 (0.2)	1.5 (0.4)	0.025
	4	1.3 (0.3)	1.5 (0.8)	NS
aPTT	1	31.9 (1.3)	31.7 (2.0)	NS
	2	32.0 (1.3)	31.7 (2.0)	NS
	3	31.8 (0.9)	31.8 (1.1)	NS
	4	31.7 (1.4)	31.4 (1.5)	NS

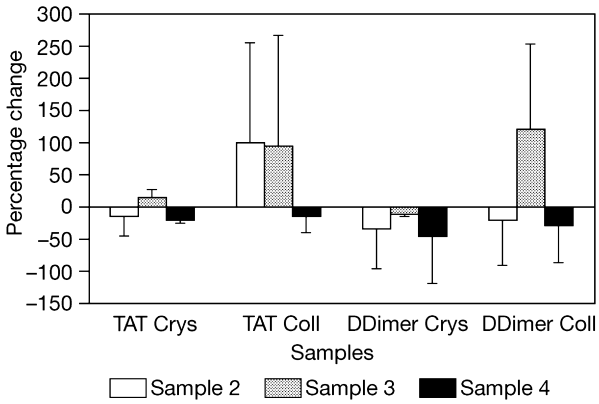

Fig 2 Difference from baseline in thrombin–antithrombin (TAT) and D-dimer values in the crystalloid (Crys) and colloid (Coll) groups. There were no significant differences between groups. Sample 1 was taken at baseline (before fluid loading); Sample 2 immediately following fluid loading and placement of regional block; Sample 3 during surgery, immediately before administration of heparin, and Sample 4 24 h after at the start of surgery. Data are mean (SD).

Discussion

In this study we have demonstrated that the previously described enhancement of coagulation by crystalloid fluid haemodilution[1–3] is present under regional anaesthesia and that it occurs before commencement of surgery. We have also shown that the effect persisted well into the operative phase, and could be demonstrated up to the time of administration of heparin.

The regional anaesthetic technique is highly effective at blocking the stress response to surgical stimulation that might normally have an effect on the enhancement of coagulation. Had the surgery produced a discernible effect on coagulation, some change in the Thrombelastograph® parameters would have been expected after the infusion of fluid and the administration of heparin (between Samples 2 and 3); however, this was not demonstrable. Indeed the colloid studied, hydroxyethyl starch 200/0.5, had almost no effect on coagulation either at the time of acute haemodilution, or during surgery. The Thrombelastograph® measures were only marginally changed by the time of heparin administration. Whilst it is possible that the colloid impaired a purely surgically induced enhancement of coagulation, this is unlikely, and it appears that the major part of the alteration in coagulation seen in the crystalloid group was attributable to the fluid administered, rather than the surgical stimulus. It is clear that enhanced coagulation in the crystalloid group occurred before commencement of surgery, and continued during the surgical stimulus. In the colloid group, the enhancement of coagulation may have been inhibited by the antiplatelet activation effect of the hydroxyethyl starches[2] through its prevention of platelet clumping. This in turn may result in the findings of non-altered coagulation in the starch group compared with the crystalloid group.

We have recently shown that the probable cause for the hypercoagulability is an imbalance between the naturally occurring anticoagulants and activated procoagulants, with a reduction in antithrombin III probably being the most important. This effect lowers the threshold above which positive feedback into the intrinsic coagulation pathway occurs, thus leading to the enhanced coagulation.[16] Of note is that this is not dependent on a mass effect, as even a relatively small decrease in anticoagulants (~20–30%) can result in this imbalance.[17 18] We have been able to demonstrate that the enhanced coagulability is induced by the rapid infusion of fluid, which alters the balance between anticoagulants and the spontaneously activated fraction of procoagulants, which by definition results in an enhancement of clot formation. It is of interest that the INR was increased at Sample 3 in the colloid group. This is a test of the extrinsic coagulation pathway, which is not measured by the Thrombelastograph®. This may be the site of action of the colloids, thus offsetting the haemodilution-induced reduction in anticoagulant factors, which is similar with both crystalloid and colloid dilution.[2]

Janvrin and colleagues[19] have previously shown an increase in coagulation and incidence of deep vein thrombosis in patients receiving crystalloid fluid during surgery. We have now taken this one step further, and have managed to define the onset of enhanced coagulation related to haemodilution *per se*. We have also demonstrated that this effect is independent of the response to surgery. It is noted that while the major part of the enhanced coagulation observed in this study was the result of the crystalloid fluid administered, we cannot totally exclude the possibility that surgical trauma resulted in the release of procoagulant factors into the systemic circulation. This in turn may have contributed to the enhanced coagulation seen in the crystalloid group. This effect appears to be modulated by the use of colloids, with no change in Thrombelastograph® values from normal after haemodilution, or surgery. This has also been previously demonstrated.[2]

While this study focuses on the intra-operative response of coagulation to fluids and surgery, it is of interest that enhanced coagulability was not demonstrated in either group 24 h after surgery. However, the lack of difference either within or between groups at 24 h (Sample 4) was not investigated, as this study was not designed, nor powered, to look at outcome variables in the postoperative period.

It is tempting to speculate that the increase in coagulation during the pre-heparin phase in the crystalloid group may lead to an increased risk of occlusive vascular events, but such a conclusion cannot be drawn on the basis of these results. However, this study does suggest that the mechanism of enhanced coagulation is related to dilution itself, and thus an imbalance between coagulants and anticoagulants, and that this is triggered by the rapid crystalloid haemodilution. Given that patients undergoing vascular surgery may be at an increased risk of coagulation, especially intra-arterial coagulation, consideration should be given to

avoiding the use of crystalloids for rapid fluid loading in vasculopathic patients undergoing surgery.

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